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Rehabilitation of oral function in head and neck cancer patients after radiotherapy with implant-retained dentures: Effects of hyperbaric oxygen therapy

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Quality of life

Summary Surgical treatment of malignancies in the oral cavity and subsequent radiotherapy often result in an anatomic and physiological oral condition unfavorable for prosthodontic rehabilitation. The objective of this prospective study was to assess the effect of hyperbaric oxygen therapy on treatment outcome (condition of peri-implant tissues, implant survival, oral functioning and quality of life) of prosthodontic rehabilitation with implant-retained lower dentures in radiated head and neck cancer patients 6 weeks and 1 year after placing the new dentures. The treatment outcome was assessed in a group of 26 head neck cancer patients who were subjected to radiotherapy after tumour surgery. Standardized questionnaires were completed and clinical and radiographic assessments were performed. After randomization, endosseous Brånemark implants were placed in the anterior part of the mandible either under antibiotic prophylaxis (13 patients) or under antibiotic prophylaxis combined with pre and postsurgery hyperbaric oxygen (HBO) treatment (13 patients). In the HBO and non-HBO group eight implants

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(implant survival 85.2%) and three implants (implant survival 93.9%) were lost, respectively. Peri-implant tissues had a healthy appearance in both groups. Osteoradionecrosis developed in one patient in the HBO group. All patients functioned well with their implant-retained lower denture. The quality of life related to oral functioning and denture satisfaction were improved to a comparable extent in the HBO and non-HBO group.

Implant-retained lower dentures can improve the quality of life related to oral functioning and denture satisfaction in head and neck cancer patients. Adjuvant hyperbaric oxygen therapy could not be shown to enhance implant survival in radiated mandibular jaw bone.

Introduction

Surgical treatment of malignancies involving the oral cavity often results in an altered anatomical situation, which may severely hamper oral functioning. Surgical treatment is often combined with radiotherapy, which further worsens oral functioning. Salivary secretion is reduced, and speech, chewing (mastication), swallowing and aesthetics are often impaired.[1–8] Due to the changed intra-oral conditions (changed anatomy, oral sequelae of radiotherapy) the possibilities to obtain proper stability and retention for a mandibular prosthesis are seriously at risk.[1,9–11] For example, particularly after radiotherapy, the load-bearing capacity of both the native and reconstructed tissues is compromised.[5,9,12,13] Until recently neither reconstructive surgery nor conventional prosthodontic techniques were capable to address these problems successfully.[14,15] In prospective studies with a follow-up of 10 years reporting on the treatment outcome of implant-retained overdentures in healthy patients suffering from impaired oral functioning due to an unstable lower denture, implant-retained overdentures have been proven to be a reliable treatment for problems involving lack of stability and retention of a lower denture.[16] Because of this high success rate a similar prosthodontic treatment approach can probably attribute to better functional results in the oral rehabilitation of head and neck cancer patients.[4,8,9,11,17–26]

Nowadays, endosseous implants are used with increasing frequency for prosthetic support in patients who are treated for malignancies in the lower region of the oral cavity.[10,12,20,26,27] Such implant-based prosthodontic rehabilitation is not only performed in patients in whom the mandible and soft tissues were reconstructed, but also in patients in whom the mandible was located in the radiation portals, in spite of the well-documented adverse biologic changes that occur when soft and osseous tissues have been exposed to ionizing radiation.[5–7,20,28–31] It has been stated that implant surgery at irradiated sites bears the significant risk of development of soft and hard tissue necrosis, and loss of implants.[32] Moreover, the appropriateness of using implants in irradiated patients has been seriously questioned.[18] To reduce these risks, the need for adjunctive prophylaxis with long lasting use of antibiotics and hyperbaric oxygen (HBO) therapy has been proposed.[33]

It was advocated to use HBO therapy prior to implant placement to improve blood flow in compromised areas. Experimental data reporting increased bone mineralization and increased biomechanical forces needed to unscrew titanium implants after HBO therapy have given support to this assumption.[34,35] Nevertheless, there is still no consensus or sound evidence in the literature concerning the benefit of HBO to improve osseointegration of dental implants in mandibles, to reduce loss of implants and to minimise risk of development of osteoradionecrosis in patients who have been treated with radiotherapy following cancer treatment.[36] Currently, the need for more detailed outcome research has brought up the issue of measuring the quality of life of cancer patients by assessing their functional status as well as their physical, social and emotional well-being through self-administered questionnaires.[37]

Therefore, the objective of this prospective study was to assess the effect of HBO therapy on treatment outcome (condition of peri-implant tissues, implant survival, oral functioning and quality of life) of prosthodontic rehabilitation with implant-retained lower dentures in irradiated head neck cancer patients.

Material and methods

Patients

In 2000 all consecutive edentulous patients that had been treated for a first malignancy in the head and neck region (squamous cell carcinoma of tongue, floor of the mouth, mandibular gingiva, buccal mucosa or oropharynx) with either radiotherapy or a combination of surgery and radiotherapy were screened to be included in this study. The patients had been admitted between 1990 and 2000 to the Head and Neck Oncology Group of the Groningen University Medical Center, the Netherlands. In total 72 patients were screened by a maxillofacial surgeon (PJS) and prosthodontist (HR). Prosthetic problems related to lack of stability and retention of the lower denture were evaluated. In addition, it was required that little or no improvement could be expected from making a new set of dentures. Forty eight of these 72 patients had problems with functioning with their lower denture. Of this group of 48 patients, 26 patients wanted to participate in this study, while the other 22 patients did not want additional non-oncologic surgical interventions as is implant placement. Patients who agreed with treatment were randomized in two groups. These patients either received peri-operative antibiotics or antibiotics in combination with HBO treatment. Informed consent was obtained from all patients.

Treatment

All patients underwent both tumour surgery and radiotherapy at the University Medical Center Groningen. Dosimetry was performed to calculate the dose at the implant locations. The cumulative absorbed dose was calculated using the CT data available for the treatment planning. The anterior part of the mandible was drawn as region of interest, the treatment plans were calculated using radiotherapy treatment-planning system, Helax-TMS 6.1B (Nucletron, The Netherlands). The maximum dose in the region of interest was used as the cumulative absorbed dose in that region (Table 1).

After randomization with regard to age, gender, site and stage of the primary tumour, reconstructive procedure and total dose of irradiation, 13 patients (group 1) received perioperative antimicrobial prophylaxis with broad-spectrum antibiotics (cefradine 1 g, three times daily during 2 weeks). The other 13 patients (group 2) received 20 HBO treatments of 100% oxygen at 2.5 atmospheres for 80 min (4 periods of 20 min) before implant surgery, and 10 HBO treatments of 100% oxygen at 2.5 atmospheres for 80 min after implant surgery in addition to the antimicrobial prophylaxis as applied in the non-HBO group. A computer program was used for randomization of the patients.[38] HBO treatments were performed at the Institute for Hyperbaric Oxygen Treatment in Hoogeveen, the Netherlands. All patients started with broad-spectrum antibiotics 1 day before implant surgery and continued for 2 weeks.

In all patients the implants (Brånemark Implants, Nobelbiocare, Gothenburg, Sweden; Table 1) were placed in the interforaminal region of the mandible as a one-stage surgical procedure by the same surgeon (GM). The most lateral implants were placed at least 5 mm medially of the mental foramen and there was an equal distance between the implants. After an osseointegration period of six months, fabrication of implant-retained prostheses was started according to standard clinical and laboratory procedures. A new maxillary complete denture and a mandibular overdenture supported by an individual made bar-clip construction were fabricated. All prostheses were made by one experienced prosthodontist (HR). Home care instructions with regard of maintenance of the prosthesis and periimplant tissues around the implants consisted of daily mechanical cleaning of the implants and connection bar

Table 1 Patient characteristics regarding age, sex, primary tumour, staging, total dose, elapsed time between radiotherapy and implant placement in years, number of implants, number of lost implants, use of HBO therapy and status

Age	Sex	Primary tumour	Stage	T_D[a]	T_I[b]	N_I[c]	I_L[d]	HBO	Status[e]
58	M	Mandibular gingiva	T_4N0	59	6	5	1	Yes	
75	M	Mandibular gingiva	T_4N0	58	1	4	–	Yes	
49	M	Mandibular gingiva	T_4N1	60	2	6	–	Yes	
63	M	Mandibular gingiva	T_4N0	61	1	4	1	Yes	Died NTR
67	F	Tongue	T_3N1	55	9	4	–	Yes	
48	M	Tongue	T_3N1	66	3	4	1	Yes	
58	M	Floor of mouth	T_4N0	60	2	4	–	Yes	
50	F	Floor of mouth	T_2N0	57	1	3	–	Yes	
58	M	Tongue/floor of mouth	T_2N2	70	10	4	–	Yes	
54	F	Tongue/floor of mouth	T_2N1	60	2	4	4	Yes	No prosthesis
50	M	Oropharynx	T_4N3	63	6	4	1	Yes	Died NTR
53	M	Oropharynx	T_2N0	52	3	4	–	Yes	Died NTR
67	F	Oropharynx	T_4N0	66	3	4	–	Yes	Died TR
68	F	Mandibular gingiva	T_4N0	60	3	5	2	No	
55	F	Mandibular gingiva	T_4N0	116	1	4	–	No	
55	M	Mandibular gingiva	T_4N1	63	1	2	–	No	
62	F	Tongue	T_2N0	64	6	4	–	No	
55	M	Tongue	T_4N0	52	3	4	–	No	
63	M	Tongue	T_3N1	46	2	4	1	No	
54	M	Floor of mouth	T_2N1	60	9	2	–	No	
58	M	Floor of mouth	T_2N1	72	8	4	–	No	Died TR
64	M	Floor of mouth	T_3N2b	60	1	4	–	No	
64	M	Oropharynx	T_4N0	50	3	4	–	No	
71	F	Oropharynx	T_4N0	50	6	4	–	No	Died TR
71	F	Tongue	T_2N1	50	3	4	–	No	Died TR
65	M	Oropharynx/base of tongue	T_4N2c	66	6	4	–	No	Died NTR

[a] T_D: cumulative dose in gray at the implant site.
[b] T_I: time interval between end of radiotherapy and placement of implants in years.
[c] N_I: number of implants.
[d] I_L: number of implants lost.
[e] Status: Died TR: died due to tumour related disease. Died NTR: died due to non-tumour related disease. No prosthesis: no implant supported prosthesis could be made because of development of osteoradionecrosis and loss of all implants.

with a soft tooth brush and interdental brushes or Superfloss (Oral B, Frankfurt am Main, Germany).

Clinical assessments

The clinical assessment included dental status, oral condition and prosthetic rehabilitation. Postoperative complications and implant survival were recorded from the time of surgery until 1 year after placement of the prostheses. Periodontal indices were assessed six weeks after placing the new dentures (T_1) and 12 months later (T_2). The periodontal indices included the following parameters: plaque index,[39] bleeding index,[39] gingival index,[40] probing depth, and implant mobility.[41] Probing depth was measured at four sites of each implant (mesially, labially, distally, lingually) by using a periodontal probe (Merit B, Hu Friedy, Chicago, USA) after removal of the bar; the distance between the marginal border of the mucosa and the tip of the periodontal probe was scored as the probing depth. Mobility of the implants was determined quantitatively by Perio Test Values, also after removal of the bar. All clinical assessments were performed by the investigator (PJS) who was not involved in treatment of the patients.

Radiographic analysis

The oblique lateral radiographic technique was used to determine resorption patterns of the edentulous mandible and to study bone (re)modeling processes following the placement of dental implants.[42] At the start of prosthetic loading (T_1) and after 12 months (T_2), four oblique lateral radiographs were made to depict the lateral and frontal parts of the mandible. The mesial/distal bone height was defined as the distance between the apex of the implant and the marginal bone level at the mesial/distal side of the implant. The measurements were executed using a specially made transparent template in which a millimetre ruler was engraved. In this way, bone height could be measured in a reproducible manner in all instances. Distances were assessed to the nearest 0.5 mm.

Functional assessments and quality of life

Preoperatively the patients (T_0) were asked to fill out questionnaires regarding oral functioning and quality of life. The questionnaires were administered by the investigator (PJS) who was not involved in treatment of the patients. Similar questionnaires had to be completed six weeks (T_1) and 12 months (T_2) after placing the new dentures. At the same time points, the patients also had to complete questionnaires regarding denture satisfaction and the impact of denture related problems on social activities:

Quality of Life (QoL) was assessed using the core questionnaire (EORTC QLQ-C30) and the head and neck module (EORTC H&N35) of the European Organization for Research and Treatment of Cancer (EORTC). The core questionnaire consisted of 30 questions (items) exploring six multi-item functional scales (physical function, role function, social function, emotional function, cognitive function, and overall health status/QoL), three multi-item symptom scales (pain, fatigue and emesis) and six single items (bowel function, breathing, appetite, sleep disorders and economic sequelae.[43] The head and neck module contained 35 items exploring symptoms and side effects of treatment. It comprised six multi-item scales (pain, swallowing, senses, speech, social eating, social contact, sexuality) and seven single items.[44] All scores ranged from 0 to 100. With regard to the functional scales of the EORTC QLQ-C30, higher scores meant higher QoL and better results. In the symptom scales and the single-item scales of the EORTC QLQ-C30, higher levels represent higher degrees of problems caused by the symptom, so that the best result in these scales was a score of 0. The scores of the H&N module finally also have a range from 0 to 100 with higher scores representing higher degrees of problems and good results showing low scores.

The physical, psychological and social impact of oral disorders was assessed using the *Oral Health Impact Profile* (OHIP) questionnaire comprising of six multi-item scales.[45,46] Responses on each item ranged from 'very often' (score 4) to 'never' (score 0). Adding the scores results in a total score per scale; a high score means a high impact on the aspect concerned. The six OHIP scales assessed were functional limitation (9 items, range 0—36), physical pain (9 items, range 0—36), physical disability (9 items, range 0—36), psychological discomfort (5 items, range 0—20), psychological disability (6 items, range 0—24) and social disability (5 items, range 0—20). In addition the OHIP-14 (14 items, range 0—56), a short form of the original OHIP-49 measuring the overall-impact of dental problems, was used.[47]

Denture satisfaction was assessed using a validated questionnaire consisting of eight separate items focusing on the function of upper and lower dentures, and on specific features such as esthetics, retention and functional comfort.[48] Each item was presented with a five point rating scale on which the patient indicated the extent he or she was (dis)satisfied. A high score indicated more dissatisfaction.

Overall denture satisfaction was expressed on a 10-point rating scale (0—10), '0' being completely dissatisfied, '10' being completely satisfied.

Subjective chewing ability was assessed by using a 9-item questionnaire on which the patient could rate on a 3-point scale her/his ability to chew different kinds of food.[49]

The impact of denture problems on social activities, such as going out, and contacting and visiting people, was assessed with the *Groningen Activity Restriction Scale Dentistry* (GARS-D).[50] GARS-D is an 11-item scale yielding a score ranging from 0 to 22; the higher the score, the larger the impact on social activities.

Data analysis

The data were evaluated using the Statistical Package Social Sciences (SPSS, version 11.5 for Windows, SPSS Inc., Chicago, USA). Changes were stated as significant if $p < 0.05$. Because the data was not normally distributed, non-parametric tests were used; the Wilcoxon signed ranks test for two related samples when comparing results within groups in time. The Mann—Whitney *U* test for two independent samples was used when comparing patients treated with and without HBO at the same time.

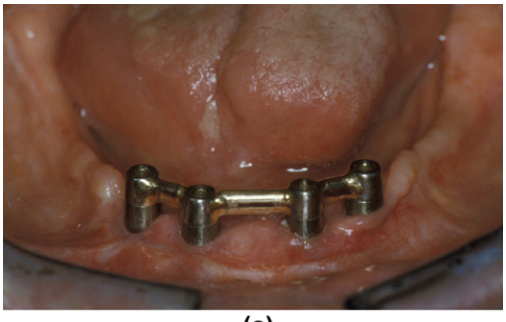
Results

Patients

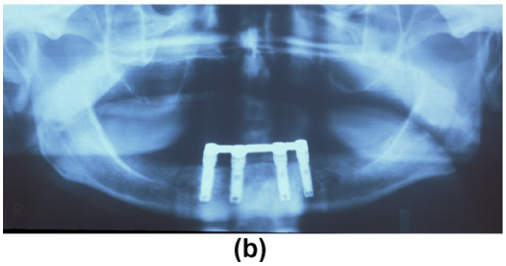
In total 26 patients, 17 men and 9 women (mean age 60.1 ± 7.5 years; range 47—77 years), were included (Table 1). The interforaminal area of the lower jaw in which the implants were inserted received a cumulative radiation dose of at least 46 Gy (mean 61.4 ± 12.9 Gy, range 46—116 Gy) at the implant site. Two patients past away during the osseointegration because of medical complications not related to the implant surgery. In 23 patients implant-retained overdentures were fabricated, while in one patient no prosthesis could be made because of loss of all implants related to development of osteoradionecrosis. At the 1 year evaluation, six patients were lost to follow-up due to serious illness not related to implant surgery.

Clinical assessments

All patients receiving HBO therapy were able to fulfill the complete treatment without problems. In all patients, the interforaminal bone volume was sufficient to enable reliable placement of implants (Fig. 1). No postoperative complications occurred related to implant surgery. Of the total 103 placed implants, 11 implants were lost in seven patients (Table 1), namely eight implants before loading and three after loading. At the one-year evaluation, in two patients treated without HBO three implants were lost (implant survival rate 93.9%) and in five patients treated with HBO eight implants were lost (implant survival rate of 85.2%). The difference between the groups was not significant. Moreover, loss of implants was not related to the time interval between radiotherapy and placement of implants.



(a)



(b)

Figure 1 A 48-years old male patient previously treated because of a T3N1 squamous cell carcinoma of the tongue with local excision of the tumour and a unilateral supra-omohyoid neck dissection. Six weeks after surgery, a fractionated radiotherapy scheme was started up to a cumulative dose of 66 Gy. Three years later four dental implants were inserted in the mandible after 20 HBO treatments before placement of the implants and 10 HBO treatments after implant surgery. In addition peri-operative antimicrobial prophylaxis with broad-spectrum antibiotics was applied. (a) Clinical intra-oral view showing the four implants connected with a bar. (b) Orthopantomogram 1.5 years after surgery showing the four implants and the bar.

No significant difference was found in percentage of successful dentures on implants between the both groups, neither existed a correlation between the reconstructive procedures (i.e. primary closure, split skin graft, soft tissue free flap or vascularized free flap), irradiation dose, implant survival and success of the denture. Osteoradionecrosis developed in one patient in the HBO group.

The mean scores on the indices for the peri-implant parameters were low at all evaluation periods and did not change significantly over time (Table 2), except for pocket-depth in the HBO group where a significant increase was observed. There was no significant difference in peri-implant health between both groups except for plaque-index at the 1-year interval.

Radiographic evaluation

During the first year after loading a minor, although significant, peri-implant bone loss of 0.7 ± 0.6 mm was observed at all implant sites (0.6 ± 0.6 mm and 0.7 ± 0.7 mm at the HBO and non-HBO sites, respectively). No significant difference in peri-implant bone loss was observed between the HBO and non-HBO patients.

Quality of life

All functional scales of the EORTC QLQ-C30 showed a strong tendency towards improvement especially in the non-HBO group, but only emotional functioning improved significantly. The symptom scales and single items showed no changes except for a temporary increase on dyspnoea at T_1 in the HBO group and a decrease on pain at T_1 in the non-HBO group (Table 3). The items of the head and neck module showed no significant changes. Also no improvement could be observed from HBO therapy on dryness of the mouth (Table 4). The results of the Oral Health Impact Profile questionnaire showed a beneficial effect of the treatment on psychological discomfort and strong tendencies towards improvement on all other scales especially in the non-HBO group (Table 5).

Functional assessments and denture satisfaction

The questionnaires regarding denture satisfaction showed significant improvement in time, but no differences between the HBO and non-HBO group were seen. The impact of denture problems on social activities, as assessed with the GARS-D, and the ability to chew different kind of foods showed tendencies towards improvement for both groups (Table 6).

Table 2 Peri-implant parameters

	HBO		Non-HBO	
	T_1	T_2	T_1	T_2
Plaque-index (score 0—3)	1.5 ± 0.8	1.7 ± 1.0	0.9 ± 0.6	0.8 ± 0.8[a]
Calculus (score 0—1)	0.0 ± 0.1	0.0 ± 0.0	0.1 ± 0.3	0.1 ± 0.3
Bleeding-index (score 0—3)	1.4 ± 0.7	1.7 ± 0.4	1.0 ± 0.6	1.6 ± 0.4
Gingiva-index (score 0—3)	0.3 ± 0.5	0.6 ± 0.8	0.4 ± 0.5	0.5 ± 0.4
Pocketdepth (mm)	2.6 ± 1.5	3.4 ± 0.9[b]	2.5 ± 0.8	3.0 ± 0.7
Width attached gingiva (score 0—3)	1.6 ± 0.9	1.5 ± 0.7	1.9 ± 0.5	1.6 ± 0.9
Periotest (scoring range: −8 to 50)	−1.8 ± 2.8	−1.2 ± 3.6	−1.1 ± 10.1	−3.1 ± 5.6

A higher score indicates more plaque, calculus, bleeding, pocketdepth, width of attached gingiva and less stability of the implant (periotest).
HBO: patients with HBO-therapy; non-HBO: patients without HBO-therapy.
T_1: six weeks after placing new dentures; T_2: twelve months after placing new dentures.
[a] Significant difference between HBO and non-HBO.
[b] Significant difference between T_1 and T_2.

Table 3 Results of the functional scales, symptom scales and single items of EORTC QLQ-C30

	HBO			Non-HBO		
	T_0	T_1	T_2	T_0	T_1	T_2
Global health status/quality of life	71.4 ± 13.5	59.4 ± 25.8	66.7 ± 13.6	79.2 ± 20.9	85.4 ± 24.3	84.3 ± 19.7
Physical functioning	82.9 ± 17.6	78.3 ± 19.1	78.1 ± 23.9	86.7 ± 14.7	84.2 ± 12.3	86.7 ± 16.7
Role functioning	85.7 ± 17.8	60.4 ± 30.8	81.0 ± 26.2	72.9 ± 36.7	87.5 ± 23.1	83.3 ± 23.6
Emotional functioning	84.5 ± 24.3	75.0 ± 22.3	91.7 ± 9.6[b]	80.2 ± 30.5	94.8 ± 11.7[c]	89.8 ± 10.8
Cognitive functioning	85.7 ± 17.8	79.2 ± 29.2	78.6 ± 18.5	87.5 ± 24.8	87.5 ± 14.8	88.9 ± 18.6
Social functioning	90.5 ± 18.9	77.1 ± 19.8	85.7 ± 26.2	77.1 ± 36.7	89.6 ± 17.7	87.0 ± 21.7
Fatigue	22.2 ± 24.8	27.8 ± 22.2	25.4 ± 22.9	12.5 ± 20.1	15.3 ± 16.7	14.8 ± 20.8
Nausea and vomiting	0.0 ± 0.0	12.5 ± 29.2	14.3 ± 24.4	0.0 ± 0.0	0.0 ± 0.0	1.9 ± 5.6
Pain	7.1 ± 18.9	18.8 ± 18.8	19.0 ± 20.2	16.7 ± 23.6	2.1 ± 5.9[a,c]	5.6 ± 11.8
Dyspnoea	0.0 ± 0.0	29.2 ± 21.4[a]	9.5 ± 16.3	20.8 ± 30.5	12.5 ± 17.3	14.8 ± 17.6
Insomnia	19.0 ± 26.2	29.2 ± 41.5	11.1 ± 27.2	20.8 ± 39.6	12.5 ± 24.8	18.5 ± 24.2
Appetite loss	14.3 ± 26.2	20.8 ± 30.5	23.8 ± 25.2	12.5 ± 24.8	4.2 ± 11.8	11.1 ± 23.6
Constipation	4.8 ± 12.6	8.3 ± 15.4	9.5 ± 25.2	8.3 ± 15.4	4.2 ± 11.8	0.0 ± 0.0
Diarrhoea	4.8 ± 12.6	8.3 ± 15.4	19.0 ± 32.5	4.2 ± 11.8	0.0 ± 0.0	3.7 ± 11.1
Financial difficulties	4.8 ± 12.6	20.8 ± 35.4	9.5 ± 16.3	16.7 ± 35.6	16.7 ± 35.6	14.8 ± 33.8

HBO: patients with HBO-therapy; non-HBO: patients without HBO-therapy.
T_0: preoperatively; T_1: six weeks after placing new dentures; T_2: twelve months after placing new dentures.
[a] Significant difference T_1 versus T_0.
[b] Significant difference T_2 versus T_1.
[c] Significant difference between HBO and non-HBO at the same point in time.

Discussion

Surgical treatment of malignancies in the oral cavity and subsequent radiotherapy often result in an anatomic and physiological oral condition unfavorable for prosthodontic rehabilitation. This unfavorable oral condition may have a negative effect on both denture satisfaction and quality of life in general. As shown in this study, many of these problems can, at least in part, be diminished by the use of an implant-retained lower denture. In this respect, the question of whether or not HBO increases implant success in irradiated patients is important. The results of this study did not show a beneficial effect of HBO with regard to implant survival and prevention of osteoradionecrosis when compared to non-HBO treated patients who received only the prophylactic antibiotics. Unfortunately, it was not possible to assess the value of prophylactic antibiotics in our patient cohort too, because it is common sense to apply antibiotic prophylaxis in patients subjected to surgical treatment (including extractions and implant placement) in irradiated areas. Although not evidence based, there is strong clinical support for the use of antibiotic prophylaxis to minimise risk of development of osteoradionecrosis.[51,52] Because of the high morbidity of osteoradionecrosis when it develops, it is for ethical reasons not allowed to perform such a control experiment in this patient cohort.

Table 4 Results of the multi-item scales and single items of EORTC QLQ-H&N35

	HBO			Non-HBO		
	T_0	T_1	T_2	T_0	T_1	T_2
Pain	9.5 ± 12.2	22.9 ± 23.9	20.2 ± 18.5	13.5 ± 17.2	9.4 ± 12.9	14.8 ± 12.3
Swallowing	28.6 ± 23.0	30.2 ± 25.9	34.5 ± 27.0	22.9 ± 15.9	16.7 ± 23.6	23.1 ± 15.5
Senses problems	23.8 ± 21.2	33.3 ± 37.8	38.1 ± 31.5	33.3 ± 28.2	27.1 ± 28.1	27.8 ± 30.0
Speech problems	6.3 ± 8.7	25.0 ± 20.4	12.7 ± 16.3	22.2 ± 27.2	18.1 ± 27.2	11.1 ± 16.7
Trouble with social eating	21.4 ± 17.9	33.3 ± 34.8	27.4 ± 17.8	36.5 ± 37.3	29.2 ± 28.9	23.1 ± 33.3
Trouble with social contact	1.9 ± 3.3	7.5 ± 14.0	6.7 ± 10.2	13.3 ± 21.7	7.5 ± 16.1	2.2 ± 3.3
Less sexuality	9.5 ± 25.2	16.7 ± 25.2	28.6 ± 35.6	31.3 ± 44.0	10.0 ± 14.9	19.0 ± 33.9
Teeth	22.2 ± 34.4	29.2 ± 27.8	28.6 ± 23.0	23.8 ± 41.8	12.5 ± 24.8	22.2 ± 33.3
Opening mouth	38.1 ± 40.5	25.0 ± 29.5	23.8 ± 25.2	37.5 ± 33.0	25.0 ± 23.6	29.6 ± 30.9
Dry mouth	52.4 ± 42.4	62.5 ± 27.8	61.9 ± 40.5	58.3 ± 46.3	54.2 ± 39.6	51.9 ± 37.7
Sticky saliva	19.0 ± 32.5	20.8 ± 30.5	23.8 ± 31.7	50.0 ± 47.1	50.0 ± 39.8	51.9 ± 33.8
Coughing	4.8 ± 12.6	16.7 ± 25.2	19.0 ± 26.2	4.2 ± 11.8	12.5 ± 17.3	14.8 ± 24.2
Felt ill	0.0 ± 0.0	16.7 ± 25.2	14.3 ± 26.2	4.2 ± 11.8	4.2 ± 11.8	7.4 ± 22.2
Pain killers	28.6 ± 48.8	25.0 ± 46.3	42.9 ± 53.5	12.5 ± 35.4	25.0 ± 46.3	22.2 ± 44.1
Nutritional supplements	28.6 ± 48.8	25.0 ± 46.3	28.6 ± 48.8	25.0 ± 46.3	37.5 ± 51.8	22.2 ± 44.1
Feeding tube	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Weight loss	0.0 ± 0.0	12.5 ± 35.4	14.3 ± 37.8	12.5 ± 35.4	12.5 ± 35.4	11.1 ± 33.3
Weight gain	0.0 ± 0.0	25.0 ± 46.3	0.0 ± 0.0	37.5 ± 51.8	0.0 ± 0.0	11.1 ± 33.3

HBO: patients with HBO-therapy; non-HBO: patients without HBO-therapy.
T_0: preoperatively; T_1: six weeks after placing new dentures; T_2: twelve months after placing new dentures.

Table 5 Results of the Oral Health Impact Profile (OHIP)

	HBO			Non-HBO		
	T_0	T_1	T_2	T_0	T_1	T_2
OHIP14	18.3 ± 9.9	20.7 ± 15.3	15.0 ± 7.3	23.9 ± 17.1	13.7 ± 14.1	12.7 ± 9.7
Functional limitation	16.9 ± 9.6	17.0 ± 8.0	14.3 ± 4.9	18.0 ± 9.3	11.7 ± 6.6	12.1 ± 7.4
Physical pain	13.6 ± 11.0	11.3 ± 8.0	8.3 ± 5.4	12.5 ± 10.3	7.9 ± 9.3	8.6 ± 5.6
Physical disability	18.3 ± 8.1	15.9 ± 12.0	16.1 ± 9.2	19.7 ± 9.7	11.0 ± 9.8	11.1 ± 9.1
Psychological discomfort	4.9 ± 4.7	4.6 ± 3.6	2.1 ± 2.1	8.3 ± 8.0	1.3 ± 2.4[a,c]	1.3 ± 1.8[b]
Psychological disability	2.7 ± 3.9	5.8 ± 5.3	2.2 ± 3.4	6.9 ± 8.4	2.8 ± 5.1	1.2 ± 2.7
Social disability	2.3 ± 3.5	3.6 ± 4.1	0.8 ± 1.6	6.5 ± 8.0	3.0 ± 5.3	1.8 ± 4.0

HBO: patients with HBO-therapy; non-HBO: patients without HBO-therapy.
T_0: preoperatively; T_1: six weeks after placing new dentures; T_2: twelve months after placing new dentures.
[a] Significant difference T_1 versus T_0.
[b] Significant difference T_2 versus T_0.
[c] Significant difference between HBO and non-HBO at the same point in time.

Table 6 Results of the functional assessments and denture satisfaction

	HBO			Non-HBO		
	T_0	T_1	T_2	T_0	T_1	T_2
GARS-D	3.1 ± 3.1	7.4 ± 7.8	5.3 ± 5.5	8.0 ± 7.9	5.3 ± 6.5	4.3 ± 7.4
Overall denture satisfaction	4.4 ± 2.3	6.8 ± 1.6	7.0 ± 2.1	4.9 ± 2.6	7.1 ± 2.6[a]	7.8 ± 1.3[b]
Denture satisfaction	28.0 ± 6.8	16.9 ± 4.6[a]	17.7 ± 6.2	26.0 ± 9.7	13.3 ± 4.3[a]	13.6 ± 4.6[b]
Chewing/eating	13.3 ± 2.5	11.6 ± 6.5	11.0 ± 5.4	13.4 ± 3.5	10.7 ± 4.8	10.0 ± 5.6

HBO: patients with HBO-therapy; non-HBO: patients without HBO-therapy.
T_0: preoperatively; T_1: six weeks after placing new dentures; T_2: twelve months after placing new dentures.
[a] Significant difference T_1 versus T_0.
[b] Significant difference T_2 versus T_0.

HBO therapy needs expensive equipment, requires significant patient compliance and involves financial costs per patient treatment. In addition, HBO therapy is not without risks and adverse effects like barotrauma, particularly of the middle ear, O_2 seizures or a change in the refractive power of the lens.[53] There are many papers written about the subject, including thorough review articles, but randomized controlled trials are lacking.[36,54] The randomized controlled trial, more than any other study design provides the most reliable evidence for treatment effectiveness.[53] Based on the available literature, no conclusions could be stated about the indications and usefulness of HBO for irradiated patients undergoing implant therapy. This is in accordance with the results of our randomized clinical trial. Although the study population of our trial is rather small, the outcome of this randomized clinical trial clearly shows that a very large population is needed to detect a clinical significant difference between HBO treated and non-HBO treated patients with regard to implant success and prophylaxis of osteoradionecrosis, if any. In this respect it even can be doubted if a randomized controlled trial with larger groups will give results in favor of HBO when looking at the tendencies in this study.

The difference in implant survival between the HBO and non-HBO treated patients as observed in this trial seems remarkable, but is mainly caused by one HBO treated patient who developed osteoradionecrosis and subsequently lost all four implants. However, also during the follow-up of the patients included in this trial beyond the observation period of this study, again patients in the HBO group tended to lose implants at a higher rate than patients treated without HBO resulting in a three years implant survival rate of 81% and 92%, respectively. Moreover, in contrast to what has been posed in the literature no relation was found between the loss of implants and the time interval between radiotherapy and placement of implants in our study.[55] However, if the observation of Granstrom that implant loss increases with time elapsed between end of radiotherapy and implant placement is real, this effect might be masked in our study by the too small sample size to confirm or reject this conclusion.

It often has been suggested that HBO may exert a positive effect on irradiation-induced oral dryness, but no clinical trials are available in the literature supporting such an assumption to date. This is in line with a study assessing the efficacy of HBO in the management of patients with radiation-induced late side effects revealing a low response rate of salivary symptoms to HBO treatment.[56] Our study confirmed the latter data as HBO treated patients reported a comparable level of oral dryness as non-HBO treated patients.

In general, we were surprised by the better performance of patients not treated with HBO on almost every aspect of this controlled trial. A possible explanation could be the extra treatment burden encompassing thirty sessions of HBO. As patients may become tired of treatment, especially when there is apparently not a very great effect to be expected on the treatment outcome, such an effect might negatively influence quality of life measurements and denture satisfaction in HBO treated patients.

In this study, a negligible effect of rehabilitation of oral function on quality of life was observed. Many of the instruments available for measuring quality of life in head and neck cancer patients are probably not sensitive enough to measure such an effect. This conclusion is in line with a recent consensus report on oral and facial rehabilitation also noting that the ''quality of life in oral and facial rehabilitation is largely unresearched. Prospective studies that quantify quality of life related to surgical measures are lacking''.[57] This observation was one of our reasons to perform our randomized clinical trial. The consensus continued ''There is an apparent need to develop and employ specific instruments for the assessment of quality of life in oral and facial rehabilitation and to apply them in prospective trials''.[57] Again this was one of the main topics of our research. Moreover, ''Health-related quality of life measurements in this respect need a specific questionnaire with appropriate sensitivity and responsiveness. This is supposed to be in addition to existing validated questionnaires tapping broader concepts, e.g. head- and neck-specific questionnaires''.[57] This was our reason for combining EORTC QLQ-C30 with EORTC H&N35, OHIP, (overall) denture satisfaction, subjective chewing ability and GARS-D. With exception of the EORTC H&N35, the more head- and neck-specific questionnaires showed some significant changes, while the applied treatment did not result in a change in the overall quality of life as measured with e.g. the EORTC QLQ-C30 and EORTC H&N35. A major reason that even the more specific questionnaires did not detect large changes in the quality of life might be that the oncology treatment, in particular radiotherapy, have resulted in so much distress and morbidity (such as worries about survival, fatigue, xerostomia, trismus, loss of taste, swallowing disorders, problems with speech) that wearing an implant-retained lower denture might have minor to no impact on overall quality of life. However, when assessing the more specific oral complaints that are related to denture problems, it was obvious that most patients reported significant improvement of their denture comfort as is obvious from the denture satisfaction scores. Thus when assessing the impact of oral treatments on the quality of life, one has to ask those questions regarding quality of life that focus on the oral component. The EORTC H&N35 seems to be not as specific as needed in this respect and the OHIP, GARS-D, denture satisfaction and chewing ability scores are just too specific for the oral component thus not reflecting an impact on the more general quality of life. Thus, there is still a need for developing more specific questionnaires addressing the impact of the oral component on quality of life.

This study shows that radiotherapy should not be considered an absolute contraindication for implant therapy in the mandible. According to our randomized clinical trial, HBO therapy does not influence the failure rate of implants inserted in mandibles when compared to patients treated without HBO therapy. Therefore, the potential benefit of preventive HBO therapy, as assumed by some authors in the literature could not be confirmed.[55,58] The latter authors based their conclusions on retrospective studies. Moreover, our findings are in line with the Cochrane review of Coulthard indicating that there is insufficient evidence for a beneficial effect of HBO with regard to implant survival.[53] Future research with larger groups of patients, probably multi-centred, should address whether there is potential benefit of hyperbaric oxygen

treatment with regard to implant survival in irradiated patients, if any. Such a beneficial effect could not be shown in our study, but the study sample was too small to make such a firm conclusion against a potential benefit of HBO therapy with regard to implant survival. Finally, one has to keep in mind that an implant-supported prosthesis is not a guarantee for uncompromised oral function after head and neck oncology treatment, but can be considered a significant factor contributing to the well-being of these patients.

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